CLAIMS

We claim:

1. A method for modulating lymphocyte activity, comprising contacting a BTLA-positive lymphocyte with a bioactive agent capable of modulating BTLA-mediated signaling in an amount effective to modulate at least one lymphocyte activity.

2. The method according to Claim 1, wherein said agent comprises an antagonist of BTLA-mediated signaling, and wherein said contacting inhibits the attenuation of lymphocyte activity mediated by BTLA signaling.

3. The method according to Claim 2, wherein said contacting increases lymphocyte activity.

4. The method according to Claim 2, wherein said antagonist comprises a blocking agent capable of interfering with the functional interaction of BTLA and B7x.

5. The method according to Claim 4, wherein said blocking agent comprises an anti-BTLA antibody capable of specifically binding to the extracellular domain of BTLA, wherein said binding interferes with the interaction of BTLA and B7x.

6. The method according to Claim 4, wherein said blocking agent comprises a soluble BTLA protein.

7. The method according to Claim 4, wherein said blocking agent comprises a soluble BTLA fusion protein.

8. The method according to Claim 4, wherein said blocking agent comprises an anti-B7x antibody capable of specifically binding to the extracellular domain of B7x, wherein said binding interferes with the interaction of BTLA and B7x.

9. The method according to Claim 4, wherein the blocking agent is selected from the group consisting of anti-BTLA antibodies, anti-B7x antibodies, BTLA polypeptides, BTLA fusion proteins, and small molecule chemical inhibitors of the interaction between BTLA and B7x.

10. The method according to Claim 1, wherein said bioactive agent comprises at least one antagonist selected from the group consisting of anti-BTLA antibodies, anti-B7x antibodies, soluble BTLA polypeptides, soluble BTLA fusion proteins, small molecule chemical inhibitors of BTLA-mediated signaling, BTLA antisense oligonucleotides, and B7x antisense oligonucleotides; and wherein said contacting increases lymphocyte activity.

11. The method according to Claim 1, wherein said agent comprises an agonist of BTLA-mediated signaling, and said contacting decreases lymphocyte activity.

12. The method according to Claim 11, wherein said agonist comprises a mimicking agent capable of mimicking the functional interaction of BTLA and B7x.

13. The method according to Claim 11, wherein said agonist comprises a mimicking agent capable of augmenting the functional interaction of BTLA and B7x.

14. The method according to Claim 12, wherein said mimicking agent comprises a soluble B7x protein capable of stimulating BTLA-4 mediated negative signaling, said B7x protein comprising the extracellular domain of B7x.

15. The method according to Claim 12, wherein said mimicking agent comprises a soluble B7x fusion protein capable of stimulating BTLA-4 mediated negative signaling, said B7x fusion protein comprising the extracellular domain of B7x.

16. The method according to Claim 11, wherein said agonist is selected from the group consisting of B7x proteins, B7x fusion proteins, small molecule chemical enhancers of BTLA-mediated signaling, and expression vectors comprising BTLA or B7x nucleic acids.

17. The method according Claim 1, wherein said lymphocyte is a T lymphocyte and said lymphocyte activity is selected from the group consisting of activation, differentiation, proliferation, survival, cytolytic activity and cytokine production.

18. The method according Claim 1, wherein said lymphocyte is a B lymphocyte and said lymphocyte activity is selected from the group consisting of activation, differentiation, proliferation, survival, and antibody production.

19. The method according to Claim 1, wherein said lymphocyte activity comprises a host immune response to a target antigen, said target antigen selected from the group consisting of a pathogen antigen, a vaccine antigen, and a tumor-associated antigen other than B7x.

20. A method for modulating the interaction of a BTLA-positive lymphocyte with a B7x-positive cell, comprising contacting a BTLA-positive lymphocyte with a bioactive agent capable of modulating BTLA-mediated signaling in an amount effective to modulate at least one lymphocyte activity.

21. The method according to Claim 20, wherein said B7x-positive cell is a tumor cell and said bioactive agent comprises an antagonist of BTLA-mediated signaling, and wherein said contacting increases the host immune response against said tumor cell.

22. The method according to Claim 21, wherein said antagonist comprises a blocking agent capable of interfering with the functional interaction of BTLA and B7x.

23. The method according to Claim 22, wherein said blocking agent comprises an anti-BTLA antibody capable of specifically binding to the extracellular domain of BTLA, wherein said binding interferes with the interaction of BTLA and B7x.

24. The method according to Claim 22, wherein said blocking agent comprises a soluble BTLA protein.

25. The method according to Claim 22, wherein said blocking agent comprises a soluble BTLA fusion protein.

26. The method according to Claim 22, wherein said blocking agent comprises an anti-B7x antibody capable of specifically binding to the extracellular domain of B7x, wherein said binding interferes with the interaction of BTLA and B7x.

27. The method according to Claim 22, wherein the blocking agent is selected from the group consisting of anti-BTLA antibodies, anti-B7x antibodies, BTLA proteins, BTLA fusion proteins, and small molecule chemical inhibitors of the interaction between BTLA and B7x.

28. The method according to Claim 21, wherein said bioactive agent comprises at least one antagonist selected from the group consisting of anti-BTLA antibodies, anti-B7x antibodies, soluble BTLA proteins, soluble BTLA fusion proteins, small molecule chemical inhibitors of BTLA-mediated signaling, BTLA antisense oligonucleotides, B7x antisense oligonucleotides, and small RNA inhibitors; wherein said antagonists inhibit the attenuation of lymphocyte activity mediated by BTLA signaling.

29. The method according to Claim 20, wherein said B7x-positive cell comprises a non-tumor non-lymphoid host cell and said agent comprises an agonist of BTLA-mediated signaling, and wherein said contacting inhibits a host immune response against said non-lymphoid non-tumor host cell.

30. The method according to Claim 29, wherein said agonist comprises a mimicking agent capable of mimicking the functional interaction of BTLA and B7x.

31. The method according to Claim 29, wherein said agonist comprises a mimicking agent capable of augmenting the functional interaction of BTLA and B7x.

32. The method according to Claim 30, wherein said mimicking agent comprises a soluble B7x protein capable of stimulating BTLA mediated negative signaling, said B7x protein comprising the extracellular domain of B7x.

33. The method according to Claim 30, wherein said mimicking agent comprises a soluble B7x fusion protein capable of stimulating BTLA-4 mediated negative signaling, said B7x fusion protein comprising the extracellular domain of B7x.

34. The method according to Claim 30, wherein said agonist is selected from the group consisting of B7x proteins, B7x fusion proteins, small molecule chemical enhancers of BTLA-mediated signaling, and expression vectors comprising BTLA or B7x nucleic acids.

35. A bioactive agent for modulating lymphocyte activity, wherein said bioactive agent comprises an antagonist of BTLA-mediated signaling which is capable of inhibiting the attenuation of lymphocyte activity mediated by BTLA signaling.

36. The bioactive agent according to Claim 35, wherein said modulation increases lymphocyte activity.

37. The bioactive agent according to Claim 35, wherein said antagonist comprises a blocking agent capable of interfering with the functional interaction of BTLA and B7x.

38. The bioactive agent according to Claim 37, wherein said blocking agent comprises an anti-BTLA antibody capable of specifically binding to the extracellular domain of BTLA, wherein said binding interferes with the functional interaction of BTLA and B7x.

39. The bioactive agent according to Claim 37, wherein said blocking agent comprises a soluble BTLA protein.

40. The bioactive agent according to Claim 37, wherein said blocking agent comprises a soluble BTLA fusion protein.

41. The bioactive agent according to Claim 37, wherein said blocking agent comprises an anti-B7x antibody capable of specifically binding to the extracellular domain of B7x, wherein said binding interferes with the functional interaction of BTLA and B7x.

42. The bioactive agent according to Claim 37, wherein said blocking agent is selected from the group consisting of anti-BTLA antibodies, anti-B7x antibodies, BTLA proteins, BTLA fusion proteins, and small molecular weight chemical inhibitors of the interaction between BTLA and B7x.

43. The bioactive agent according to Claim 35, wherein said bioactive agent comprises at least one antagonist selected from the group consisting of anti-BTLA antibodies, BTLA proteins, BTLA fusion proteins, small molecule chemical inhibitors of BTLA expression or BTLA-mediated signaling, BTLA antisense oligonucleotides, and small RNA inhibitors.

44. A bioactive agent for modulating lymphocyte activity, wherein said bioactive agent comprises an agonist of BTLA-mediated signaling, and said modulation decreases lymphocyte activity.

45. The bioactive agent according to Claim 44, wherein said agonist comprises a mimicking agent capable of mimicking the functional interaction of BTLA and B7x.

46. The bioactive agent according to Claim 44, wherein said agonist comprises a mimicking agent capable of augmenting the functional interaction of BTLA and B7x.

47. The bioactive agent according to Claim 45, wherein said mimicking agent comprises a B7x protein capable of stimulating BTLA-4 mediated negative signaling, said B7x protein comprising the extracellular domain of B7x.

48. The bioactive agent according to Claim 45, wherein said mimicking agent comprises a B7x fusion protein capable of stimulating BTLA-4 mediated negative signaling, said B7x fusion protein comprising the extracellular domain of B7x.

49. The bioactive agent according to Claim 44, wherein said agonist is selected from the group consisting of B7x proteins, B7x fusion proteins, small molecule chemical enhancers of BTLA-mediated signaling, expression vectors comprising BTLA nucleic acids, and expression vectors comprising B7x nucleic acids.

50. A method for treating cancer in a patient having B7x-positive tumor cells comprising administering to the patient an antagonist of BTLA-mediated signaling, wherein said administration is effective to increase the host immune response against said B7x-positive tumor cell.

51. The method according to Claim 50, wherein said antagonist comprises a blocking agent capable of interfering with the functional interaction of BTLA and B7x.

52. The method according to Claim 51, wherein said blocking agent comprises an anti-BTLA antibody capable of specifically binding to the extracellular domain of BTLA, wherein said binding interferes with the interaction of BTLA and B7x.

53. The method according to Claim 51, wherein said blocking agent comprises a soluble BTLA protein.

54. The method according to Claim 51, wherein said blocking agent comprises a soluble BTLA fusion protein.

55. The method according to Claim 51, wherein said blocking agent comprises an anti-B7x antibody capable of specifically binding to the extracellular domain of B7x, wherein said binding interferes with the interaction of BTLA and B7x.

56. The method according to Claim 51, wherein the blocking agent is selected from the group consisting of anti-BTLA antibodies, anti-B7x antibodies, BTLA proteins, BTLA fusion proteins, and small molecule chemical inhibitors of the interaction between BTLA and B7x.

57. The method according to Claim 50, wherein said bioactive agent comprises at least one antagonist selected from the group consisting of anti-BTLA antibodies, soluble BTLA proteins, soluble BTLA fusion proteins, small molecule chemical inhibitors of BTLA expression or BTLA-mediated signaling, BTLA antisense oligonucleotides, B7x antisense oligonucleotides, and small RNA inhibitors; wherein said antagonists inhibit the attenuation of lymphocyte activity mediated by BTLA signaling.

58. A method for treating a patient having an autoimmune disease characterized by the presence of autoreactive BTLA-positive lymphocytes, comprising administering to the patient an agonist of BTLA-mediated signaling, wherein said administration is effective to inhibit an autoreactive immune response against non-lymphoid non-tumor host cells expressing B7x.

59. The method according to Claim 58, wherein said agonist comprises a mimicking agent capable of mimicking the functional interaction of BTLA and B7x.

60. The method according to Claim 58, wherein said agonist comprises a mimicking agent capable of augmenting the functional interaction of BTLA and B7x.

61. The method according to Claim 59, wherein said mimicking agent comprises a soluble B7x protein capable of stimulating BTLA mediated negative signaling, said B7x protein comprising the extracellular domain of B7x.

62. The method according to Claim 59, wherein said mimicking agent comprises a soluble B7x fusion protein capable of stimulating BTLA mediated negative signaling, said B7x fusion protein comprising the extracellular domain of B7x.

63. The method according to Claim 58, wherein said agonist is selected from the group consisting of B7x proteins, B7x fusion proteins, small molecule chemical enhancers of BTLA-mediated signaling, and expression vectors comprising BTLA or B7x nucleotides.

64. A recombinant BTLA nucleic acid, comprising a nucleotide sequence having at least about 70% identity to the nucleotide sequence set forth in SEQ ID NO:7 or 9.

65. A recombinant BTLA nucleic acid, which will hybridize under moderately or highly stringent conditions to a nucleic acid comprising the nucleotide sequence set forth in SEQ ID NO:7 or 9 or the complement thereof.

66. A recombinant BTLA nucleic acid, comprising a nucleotide sequence complementary to the nucleotide sequence of the recombinant BTLA nucleic acid of claim 64 or 65.

67. The recombinant BTLA nucleic acid of claim 64 or 65, comprising a splice variant of the nucleotide sequence set forth in SEQ ID NO:7 or 9.

68. The recombinant BTLA nucleic acid of claim 64 or 65, comprising an allelic variant of the nucleotide sequence set forth in SEQ ID NO:7 or 9.

69. The recombinant BTLA nucleic acid of claim 64 or 65, which encodes a BTLA protein capable of interacting with B7x.

70. The recombinant BTLA nucleic acid of claim 64 or 65, which encodes a BTLA protein having BTLA signaling activity.

71. The recombinant BTLA nucleic acid of claim 64 having the nucleotide sequence set forth in SEQ ID NO:7 or 9.

72. The recombinant BTLA nucleic acid of claim 64 or 65, comprising a double-stranded RNA capable of inducing RNA interference and inhibiting BTLA expression in a cell that expresses BTLA.

73. A recombinant BTLA nucleic acid, encoding a BTLA protein comprising the amino acid sequence set forth in SEQ ID NO:8 or 10.

74. An expression vector, comprising the recombinant BTLA nucleic acid according to any one of claims 64, 65, 69 and 70 operably linked to regulatory sequences recognizable by a host cell transfected with the recombinant BTLA nucleic acid.

75. A host cell, comprising the recombinant BTLA nucleic acid according to any of claims 64, 65, 69 and 70.

76. A host cell, comprising the expression vector of claim 74.

77. A process for producing a BTLA protein, comprising culturing the host cell of claim 76 under conditions suitable for the expression of BTLA protein.

78. The process of claim 77, further comprising isolating the BTLA protein.

79. A BTLA protein produced by the process of claim 78.

80. An isolated BTLA protein, comprising an amino acid sequence encoded by the recombinant BTLA nucleic acid of any of claims 64, 65, 69 and 70.

81. An isolated BTLA protein, comprising an amino acid sequence having at least about 70% identity to the amino acid sequence set forth in SEQ ID NO:8 or 10.

82. The isolated BTLA protein of claim 81, comprising an extracellular V-like Ig domain, a transmembrane region, and an intracellular domain of approximately 100 amino acids that comprises a Grb2 interaction site and two ITIM sequences.

83. The isolated BTLA protein of claim 81, which is capable of interacting with B7x.

84. The isolated BTLA protein of claim 81, which is capable of interacting with SHP-1, SHP-2, or both SHP-1 and SHP-2.

85. The isolated BTLA protein of claim 81, which has BTLA signaling activity.

86. The isolated BTLA protein of claim 81, which is capable of inhibiting lymphocyte activity.

87. The isolated BTLA protein of claim 81, comprising the amino acid sequence set forth in SEQ ID NO:8 or 10.